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EDITORIAL COMMENT

"Crying Fire in a Theater" or a "Confirmatory Sighting?"*

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How should the cardiology community respond when informed of an apparent considerable increase in mortality from a procedure when data are derived from the only randomized trial assessing the question, but that trial is small, the analysis post-hoc, and the result somewhat counterintuitive? That is the question raised by the report by Vermeersch et al. (1) in this issue of the *Journal* in describing an excess risk of late death after sirolimus-eluting stent (SES) placement in patients with diseased saphenous vein grafts (SVG), a group comprising 5% to 8% of all patients undergoing percutaneous coronary intervention. The importance of the question is magnified considering the fact that we are speaking of drug-eluting stents (DES), devices implanted in nearly 2 million patients annually worldwide and for which other major safety questions have arisen recently (2–4).

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The SES and paclitaxel-eluting stents were approved for use in Europe and the U.S. on the basis of short-term results in highly selected patients, whose characteristics apply only to approximately 40% of patients undergoing stenting worldwide. Important subgroups of patients were excluded, including those with acute myocardial infarction, need for multivessel or complex stenting, those with restenosis and, germane to this discussion, those needing treatment of diseased SVG.

Four-year outcomes in the well-studied "on-label" types of patients generally have been reassuring, with carefully considered meta-analyses showing a modest excess risk of late stent thrombosis offset by a reduction in restenosis-related adverse events and an overall neutral effect on the end point of death and myocardial infarction. Need for late revascularization was markedly diminished (5).

Unanswered concern, however, has arisen regarding long-term adverse outcomes for the "off-label" group (2–4). Pathophysiologic underpinnings of these clinical outcomes have been suggested to involve delayed reendothelialization of the coronary artery after DES placement leading to stent thrombosis (6), sirolimus activation of tissue factor (7) (likely a greater propensity for this in SVG? [8]), and perhaps diminished capacity to develop collateral vessels in the event of reblockage (9).

Into this mix are placed the results of the RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent) study (1). Attempting to circumvent the inevitable biases confounding interpretation of nonrandomized studies, the investigators commendably attempted to scientifically address the question as to whether or not the Cypher SES (Cordis, Johnson & Johnson, Miami Lakes, Florida) reduces angiographic restenosis (late lumen loss) 6 months after stenting, in comparison with bare-metal stenting, in patients with de novo SVG lesions (10). The patient population was notable for well-preserved left ventricular function and the absence of recent myocardial infarction, among other things. Non-cardiac exclusions were limited to creatinine >3.0 mg/dl. Only 75 patients were required to achieve 80% power for the primary end point. Prespecified secondary end points were somewhat numerous, but none, either in the report or clinicaltrials.gov submission, extended beyond 6 months. Late loss and target lesion/vessel revascularization were all significantly reduced with the SES, and no adverse safety signal was noted (10).

Prompted by the aforementioned recent safety concerns (2–4), the authors obtained permission to evaluate these patients for a longer period of time. Over an average two and a half year follow-up, 11 of 38 SES patients died, compared with 0 of 37 in the bare-metal stent group ($p < 0.001$) (1). One death was directly due to stent thrombosis when the patient was off antiplatelet therapy for surgery, 3 were out-of-hospital sudden deaths while taking at least one antiplatelet agent, and another occurred after redo bypass surgery for restenosis and progressive disease elsewhere. Of the patients with sudden cardiac death, ejection fractions were 70%, 32%, and 75%, suggesting that, at least for 2 patients, scar-related arrhythmia was an unlikely cause (thereby increasing the likelihood of a stent thrombosis-mediated event). Other deaths could not be directly ascribed in any way to the SES. Fisher exact test for 5 versus 0 stent-related events yielded a p value of 0.054.

These results should not be viewed out of context, nor can they be ignored. In this instance, a somewhat-informal Bayesian approach is preferred, considering the likelihood of excess risk based upon prior data, and then factoring in the scientific merit of the present publication. Pathobiology should be considered, but emotion (and there is a lot of it in this field) and intuition should be downplayed. One should only recall that we once thought that premature ventricular

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complexes should be suppressed to eliminate serious ventricular tachycardia and sudden death, to understand that intuition is not always correct in our field.

Previous fully peer-reviewed and published data on the use of SES for de novo SVG lesions is limited to uncontrolled registries (11,12). No evidence of excess mortality beyond expected has been reported.

That said, it is obvious and appropriate to call for more scientifically rigorous data on this important subset of patients. Logistical and financial challenges will make this difficult. It is quite possible, if not likely, that there is no excess risk. In the meantime, however, the cautious physician might well wish to refrain from using SES in SVG whose closure might be expected to lead to a large infarction. Current data, however limited, do not suggest an excess stent thrombosis risk when DES are applied to in-stent restenosis (13).

Finally, there are a number of "big-picture" lessons that should be learned from this and similar instances. First, the U.S. Food and Drug Administration should require larger trials, with broader entry criteria better reflecting the type of patients who might be treated once devices are approved, for trials intended for device approval recommendation. Second, one must not overreact to the outcome of a study that it was not specifically designed to address. Such outcomes should be considered hypothesis generating. At the same time, the paucity of appropriate trial data tends to exaggerate the importance of whatever data we might have and, importantly, physicians must treat their patients on the basis of the best available data, however flawed it might be. Third, and this criticism is not at all levied at the authors of this particular report, it is the serious responsibility of the investigator to educate the media in a balanced fashion about their results so that patients attempting to inform themselves and become involved in their own medical decisions are not misled. This, unfortunately, has not always been the case recently.

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